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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-10,12,13,20,28-30,33-35 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-10,12,13,20,28-30,33-35 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10/30/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2007 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 8-10, 12-13, 20, 28-30, 33-35 and 40-43 are presently pending for examination.

Claim Rejections - 35 USC § 103

4. Claims 1, 8-10, 12-13, 20, 28-30 and 33-35 remain and claims 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. (US Patent No. 6,512,161; or WO 99/35241 A1; see IDS of 4-07-06; citations given for US Patent), and Eggerman et al. (See IDS of 4-06-05) in view of GenBank Accession No NM_000384 (Huang et al. Reference #1), Monia et al. (US 5,656,612; see Reference A of PTO-892 mailed 1/14/2003), Agrawal et al. (2000, see Reference U of PTO-892 mailed 1-13-2004), and Wengel et al. (US 2002/0068708A1), for the reasons of record.

Applicant's arguments filed 10/30/2007 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that none of the

cited references either alone or in combination, suggests to the artisan of ordinary skill that non-catalytic oligonucleotide compounds should be fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3 excluding the start codon region as recited by the pending claims. Moreover, Applicants assert that Agrawal et al. teaches away from excluding the start codon region, further demonstrating the non-obviousness of the claims.

Based upon Applicant's assertions, it appears that the heart of Applicant's traversal relies upon notion that the cited references would not lead the ordinary skilled artisan to design antisense oligonucleotides which exclude the start codon region of apolipoprotein B mRNA. Contrary to Applicant's assertions, first it is noted that the design of antisense oligonucleotides which exclude the start codon region is not a novel feature of the invention described in the specification as filed. Applicant's introduction of this limitation into the claims, was only necessitated by the desire by Applicants to design around the prior art. Applicant's specification describes the "start codon" (or "translation initiation codon"), the coding region, intron/exon junctions, and the termination codon as being preferred targets for designing antisense compounds, therefore to assert that designing antisense compounds which specifically exclude the start codon would render the claimed invention novel over the prior art, appears to contradict Applicant's own disclosure (see paragraphs [0027]-[0030] of the published patent application). Moreover, the fact that Applicants suggest that antisense compounds can be designed to target the start codon region, the coding region, intron/exon junctions or the termination codon region, suggests a level of flexibility in

design choice. In other words, that the skilled artisan would expect to produce functional antisense oligonucleotides which target the start codon region, the coding region, intron/exon junctions or the termination codon region.

Moreover, to assert that the disclosure of Agrawal et al. teaches away from the claimed invention (§ C of the reply filed 10/30/2007) is to assert that Applicant's own specification teaches away from the claimed invention, since both teach that one of the preferred target sites includes the start codon, among other preferred sites, such as the 5' and 3' UTR, the coding region, and intron/exon junctions.

5. Applicants, at page 7-8 of the reply filed 10/30/07 (§ B), argue that because Eggerman et al. and Rouy et al. describe antisense compounds that are not targeted to any particular region to target apolipoprotein B, which these references neither teach nor suggest that the antisense oligonucleotides should exclude the start codon region.

6. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

7. At page 11 of Applicant's response (§ D), Applicant's assert that none of the cited references teach or suggest a colloidal dispersion system as recited in instant claim 13.

8. Contrary to Applicant's assertions, Rouy et al. teach the use of "'pharmaceutically acceptable carrier' comprises diluents and fillers which are pharmaceutically acceptable for methods of administration, are sterile, and may be *aqueous or oleaginous*

suspensions formulated using suitable dispersing or wetting agents and suspending agents." Moreover, Monia et al. describe a variety of suitable carriers or formulations as pharmaceutically acceptable carriers, see e.g. col. 7, lines 41-59:

> Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.
>
> Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable.
>
> Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives.
>
> In addition to such pharmaceutical carriers, cationic lipids may be included in the formulation to facilitate oligonucleotide uptake. One such composition shown to facilitate uptake is Lipofectin (BRL, Bethesda Md.).

Wengel et al. teach the use of a carrier system to enhance cellular uptake, and Agrawal et al. teach the use of complexes of polycations and negatively charged oligonucleotides to facilitate cellular internalization of the oligonucleotides.

Since Applicants do not adequately define what is intended to be encompassed by the term "colloidal dispersion system," absent evidence to the contrary the carrier systems disclosed by the prior art cited reads on the claimed invention.

9. At page 11 of the reply filed 10/30/2007 (§ E), Applicants assert that the cited references do not teach or suggest the limitations of claims 29-30. In addition, Applicants noted that "*the cited references additionally fail to teach or suggest the specific regions of SEQ ID NO: 4 recited by claim 29 and claim 30.*"

10. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies

(i.e., that the cited references fail to teach the specific regions of SEQ ID NO: 4) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

11. As stated in the prior Office Action, one of ordinary skill in the art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the apolipoprotein B gene as defined by SEQ ID NO: 3 of the instant specification, since GenBank Accession No. NM_000384 clearly set forth the nucleotide sequence of SEQ ID NO: 3 as the sequence encoding the full-length apolipoprotein B mRNA. Moreover, NM_000384 clearly defines the 5'-UTR as occurring before nucleotide 129, start codon region as beginning at nucleotide 129, and the coding sequence as extending from nucleotide 129 to nucleotide 13820, therefore the 3' UTR would be defined as the remaining sequence corresponding to nucleotides 13821 through 14121. Moreover, according to Agrawal et al., if the nucleotide sequence of a gene was known, designing antisense oligonucleotides to target the various regions of that gene, including the 5' UTR, *specifically nucleotides 1-128 of SEQ ID NO: 3,* the coding sequence, *which extends from nucleotide 129 through 13820 of SEQ ID NO: 3,* and the 3' UTR, nucleotides 13821 through 14121 of SEQ ID NO: 3, as suggested by Agrawal et al., would allow the ordinary skilled artisan to further elucidate the role of a target gene of interest (apolipoprotein B, as suggested by Eggerman et al. and Rouy et al.) in various cellular processes.

One of ordinary skill in the art would have been motivated to design compounds of 12 to 30 nucleobases in length since Rouy et al. expressly teaches antisense oligonucleotides targeting apolipoprotein B mRNA comprising at least 20 nucleobases in length. Moreover, one of ordinary skill in the art would have been motivated to design oligonucleotide compounds targeting apolipoprotein B mRNA comprising one or more sugar modifications, phosphorothioate modified internucleoside linkages, and 5'-methylcytosine modified nucleobases, since Monia et al. teaches that these modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. Moreover, Monia et al. teach that oligonucleotides comprising these modifications possess high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides. Furthermore, one of ordinary skill in the art at the time of the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards exonucleolytic degradation, effective delivery into cells, and display unprecedented binding affinity to both RNA and DNA (see Wengel et al., page 3, lines 25-35).

It would have been obvious to the ordinary skilled artisan to combining prior art elements of Monia et al., Agrawal et al., and Wengel et al. with the teachings of Rouy et al. and Eggerman et al. according to known methods to yield predictable results, specifically to protect the modified antisense oligonucleotides of Rouy et al. and

Eggerman et al. from nuclease degradation, increase hybridization efficiency, and increase cellular uptake of the modified antisense oligonucleotide.

12. Claims 1, 8-10, 12-13, 20, 28, 29-30, 33-35, and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. (US Patent No. 6,512,161; or WO 99/35241 A1; see IDS of 4-07-06; citations given for US Patent), and Eggerman et al. (See IDS of 4-06-05) in view of GenBank Accession No NM_000384 (Huang et al. Reference #1), Monia et al. (US 5,656,612; see Reference A of PTO-892 mailed 1/14/2003), Agrawal et al. (2000, see Reference U of PTO-892 mailed 1-13-2004), and Wengel et al. (US 2002/0068708A1), as applied to claims 1, 8-10, 12-13, 20, 28, 29-30, 33-35 above, and further in view of Bennett et al. (US 6,172,216).

The teachings of Rouy et al. (US Patent No. 6,512,161; or WO 99/35241 A1; see IDS of 4-07-06; citations given for US Patent), and Eggerman et al. (See IDS of 4-06-05) in view of GenBank Accession No NM_000384 (Huang et al. Reference #1), Monia et al. (US 5,656,612; see Reference A of PTO-892 mailed 1/14/2003), Agrawal et al. (2000, see Reference U of PTO-892 mailed 1-13-2004), and Wengel et al. (US 2002/0068708A1), as set forth above are incorporated here, however the cited references do not teach antisense compounds as recited in instant claim 40.

Bennett et al. teach that the incorporation of modified nucleobases into oligomeric compounds, including 5-methylcytosine modifications, is well known in the art for the purpose of increasing the binding affinity of the oligomeric compounds of the invention. (col. 9, lines 5-7). Bennett et al. also discloses wherein the oligonucleotide is a chimeric oligonucleotide, comprising 2'-MOE modifications (other positions comprise

2'-deoxy modifications), all 2'-MOE cytosines are 5-methylcytosines, and all linkages are phosphorothioate linkages. In Example 5 of Bennett et al. the following is disclosed:

> Chimeric oligonucleotides, oligonucleosides or mixed oligonucleotides/oligonucleosides of the invention can be of several different types. These include a first type wherein the "gap" segment of linked nucleosides is positioned between 5' and 3' "wing" segments of linked nucleosides and a second "open end" type wherein the "gap" segment is located at either the 3' or the 5' terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as "gapmers" or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as "hemimers" or "wingmers".

Bennett et al. also teaches that antisense compounds may encompass any pharmaceutically acceptable salt, which upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Moreover, the pharmaceutically acceptable salts of Bennett et al. encompass "salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto." Therefore, the disclosure of Bennett et al. encompasses oligomeric compounds comprising sodium salts; see for example, col. 11, lines 1-23. Additionally, Bennett et al. teach the pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.

Bennett et al. further teach that "colloidal dispersion systems" may be used as delivery vehicles to enhance the in vivo stability of the compounds and/or to target the compounds to a particular organ, tissue or cell type. Colloidal dispersion systems

include, but are not limited to, macromolecule complexes, nanocapsules, microspheres, beads and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, liposomes and lipid:oligonucleotide complexes of uncharacterized structure. A preferred colloidal dispersion system is a plurality of liposomes."

The modified therapeutic oligonucleotides of Bennett et al. are disclosed as having increased nuclease stability and increased cellular uptake.

13. The teachings of Eggerman et al. and Rouy et al. clearly teach antisense oligonucleotides targeting apolipoprotein B mRNA, and further wherein said antisense oligonucleotides are 20 nucleobases in length, and comprise modifications that increase the functional properties of the modified oligonucleotides. Moreover, the prior art clearly discloses the nucleotide sequence of apolipoprotein B as set forth in SEQ ID NO: 3 recited in the instant claims, and clearly provides a suggestion to modify antisense oligonucleotides targeting apolipoprotein B (see Rouy et al.) to increase the cellular activity of the oligonucleotides in a cellular environment, these modifications are expected to produce a predictable increase in nuclease stability, hybridization affinity, and an increase in cellular uptake of oligonucleotides comprising the modifications as taught by Monia et al., Bennett et al., Wengel et al., and Agrawal et al. Moreover, Bennett et al. provides clear teaching, suggestion, and motivation to modify the antisense compounds of Rouy et al. and Eggerman et al. to comprise pharmaceutically acceptable salts, since the use of antisense compounds in combination with these salts retain the desired biological activity of the parent compound in a physiological environment.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE